

A Single High-Fat Meal Adversely Affects Postprandial Vascular Endothelial Function: A Systematic Review and Meta-Analysis of Clinical Trials

Juanita J. Fewkes

Online Supplementary Material

ONLINE SUPPLEMENTARY MATERIAL

**A Single High-Fat Meal Adversely Affects Postprandial Vascular Endothelial Function:
A Systematic Review and Meta-Analysis of Clinical Trials.**

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Supplementary Table 1. Full search strategy and search terms in Ovid MEDLINE

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R): 1946 to 20 January 2022
1. high adj2 fat*.mp
2. High fat*.mp
3. oral fat load.mp
4. lipid*.mp
5. triglyceride*.mp
6. dietary fat*.mp
7. MeSH exp Lipids/
8. MeSH exp Dietary Fats/
9. MeSH Diet, High-Fat/
10. MeSH exp Triglycerides/
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. postprandial*.mp
13. post prandial*.mp
14. same day.mp
15. post meal*.mp
16. post cibal*.mp
17. postcibal*.mp
18. after the meal.mp
19. time course.mp
20. acute hypertriglyceridemia.mp
21. MeSH exp Postprandial Period/
22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. endotheli*.mp
24. forearm blood flow*.mp
25. brachial arter*.mp
26. flow mediated dilat*.mp
27. flow mediated vasodilat*.mp
28. flow mediated vasoactivit*.mp
29. FMD.mp
30. MeSH exp Endothelium, Vascular/
31. MeSH exp Brachial Artery/
32. reactive hyper?emia.mp
33. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 11 and 22 and 33
Note: exp, exploded; MeSH, Medical Subject Headings; mp, multi-purpose

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Supplementary Table 2. A summary of the characteristics of the studies included in the systematic review.

	All included	NO-Dependent FMD
Study Design		
RCT (studies)	83	62
Non-RCT (studies)	48	28
Cross Over (studies)	66	49
Parallel (studies)	17	13
Participant Characteristics		
Sample Size Median (participants)	15	14
Sample Size Range (participants)	5-93	6-93
Sample Size IQR (participants)	10-20	10-20
Total participants	4061	2856
≤20 participants in study (%)	76.4	80.5
Age Average (years)	41.0	41.2
Age Range (years)	20.0-68.4	20.0-68.4
BMI Median (kg/m ²)	25.8	25.9
BMI Range (kg/m ²)	20.5-45.1	23.8-29.2
BMI IQR (kg/m ²)	23.6-28.9	21.9-45.1
Male-only (studies)	47	35
Female-only (studies)	7	5
Mixed sex (studies)	73	48
Sex not reported (studies)	4	2
Healthy (participants)	1838	1258
CVD Risk (participants)	2062	1549
CVD disease (participants)	161	49
Total CVD or risk (participants)	2223	1598
Challenge Meal Contents		
Fast Food (studies)	22	16
Cream-based (studies)	32	16
Pastry/Sandwich (studies)	31	25
Milkshake/Smoothie (studies)	13	10
Soup (studies)	5	4
Dinner meal (studies)	5	5
Breakfast meal (studies)	6	4
Not Reported (studies)	17	10

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	All included	NO-Dependent FMD
Energy Breakdown		
Total Fat (g)	66.3	64.1
Total Fat (En%)	59.5	58.5
Total Carbohydrate (g)	70.0	72.0
Total Carbohydrate (En%)	28.5	29.0
Total Protein (g)	25.5	24.0
Total Protein (En%)	10.5	10.5
Total Energy (kJ)	4197	4145
Postprandial FMD measurement time points		
1-hour (studies)	27	20
2-hour (studies)	111	85
3-hour (studies)	70	53
4-hour (studies)	136	91
5-hour (studies)	15	10
6-hour (studies)	44	24
7-hour (studies)	1	0
8-hour (studies)	18	11
FMD Analysis Method		
Manual measurement (studies)	61	33
Edge detection (studies)	70	57
Risk of Bias		
Low Risk, RCT (studies)	5	5
Some Concerns, RCT (studies)	57	51
High Risk, RCT (studies)	21	6
Low Risk, Non-RCT (studies)	0	0
Moderate Risk, Non-RCT (studies)	29	14
Serious Risk, Non-RCT (studies)	19	14
Critical Risk, Non-RCT (studies)	0	0

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; En%, percentage of total meal energy; FMD, flow-mediated dilation; non-RCT, non-randomised controlled trial; RCT, randomised controlled trial.

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Supplementary Table 3. Other multivariable models depicting the meta-regression analysis

exploring the effect of moderator covariates on FMD% effect-size variation between studies.

Covariate	Slope	Standard Error	Z-value	2-sided P-value	95% CI Lower	95% CI Upper	Obs (N)	R ²	R ²
2-hour model 2									
Intercept	-137.07	57.37	-2.39	0.017	-249.51	-24.64	79	87.02	0.409
BMI (kg/m ²)	-0.14	0.05	-3.12	0.002	-0.24	-0.05			
Fasting FMD%	-0.28	0.08	-3.63	0.000	-0.43	-0.13			
Total Energy (kJ)	0.00	0.0001	0.06	0.950	-0.00	0.00			
Total Fat (En%)	0.02	0.01	1.49	0.136	-0.01	0.04			
Sample Size (N)	0.03	0.02	1.43	0.152	-0.01	0.07			
Male N (%)	-0.00	0.00	-0.59	0.555	-0.01	0.01			
Year	0.07	0.03	2.45	0.014	0.01	0.13			
2-hour model 3									
Intercept	-138.63	56.88	-2.44	0.015	-250.11	-27.15	80	86.97	0.407
Age (years)	-0.00	0.02	-0.04	0.967	-0.03	0.03			
BMI (kg/m ²)	-0.15	0.06	-2.37	0.018	-0.27	-0.03			
Fasting FMD%	-0.28	0.08	-3.54	0.000	-0.44	-0.13			
Total Energy (kJ)	0.00	0.00	0.12	0.905	-0.00	0.00			
Total Fat (En%)	0.02	0.01	1.78	0.075	-0.00	0.04			
Sample Size (N)	0.03	0.02	1.32	0.187	-0.01	0.06			
Year	0.07	0.03	2.50	0.013	0.02	0.13			
2-hour model 4									
Intercept	-124.69	57.55	-2.17	0.030	-237.49	-11.89	79	87.42	0.382
Age (years)	0.00	0.02	0.05	0.958	-0.03	0.03			
BMI (kg/m ²)	-0.14	0.06	-2.16	0.031	-0.26	-0.01			
Fasting FMD%	-0.29	0.08	-3.57	0.000	-0.44	-0.13			
Total Energy (kJ)	0.00	0.00	0.15	0.880	-0.00	0.00			
Total Fat (En%)	0.02	0.01	1.62	0.105	-0.00	0.04			
Male N (%)	-0.00	0.00	-0.23	0.815	-0.01	0.01			
Year	0.06	0.03	2.23	0.026	0.01	0.12			
3-hour model 2									
Intercept	-93.03	55.75	-1.67	0.095	-202.31	16.24	53	64.57	0.677
Fasting FMD%	-0.27	0.07	-3.81	0.000	-0.40	-0.13			
Total Energy (kJ)	0.00	0.00	0.96	0.335	-0.00	0.00			
Total Fat (En%)	-0.03	0.01	-2.51	0.012	-0.05	-0.01			
Sample Size (N)	-0.01	0.02	-0.30	0.767	-0.05	0.04			
Year	0.05	0.03	1.71	0.087	-0.01	0.10			

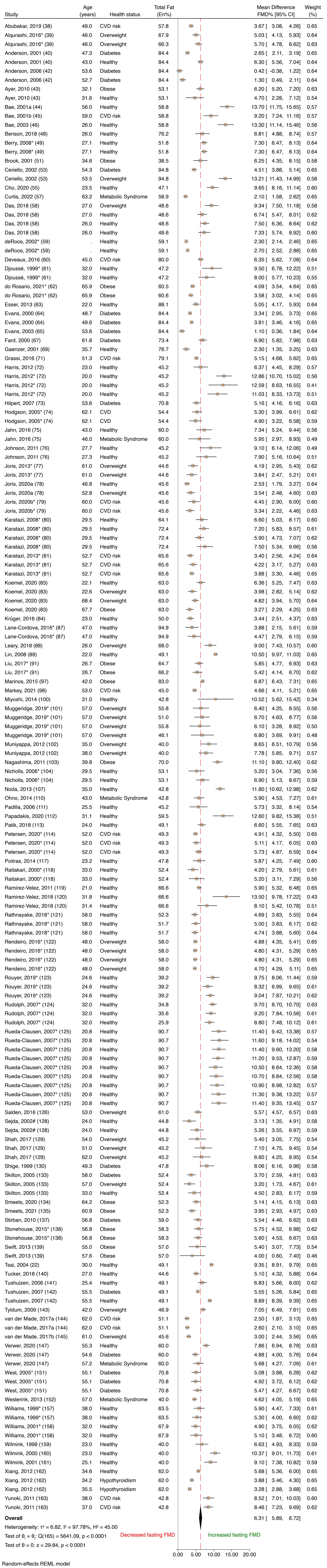
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Covariate	Slope	Standard Error	Z-value	2-sided P-value	95% CI Lower	95% CI Upper	Obs (N)	I^2	R^2
4-hour model 2									
Intercept	0.15	1.55	0.09	0.925	-2.89	3.18	85	89.63	0.367
Age (years)	-0.02	0.02	-1.19	0.233	-0.05	0.01			
BMI (kg/m^2)	0.07	0.06	1.18	0.236	-0.04	0.18			
Fasting FMD%	-0.28	0.07	-4.22	0.000	-0.40	-0.15			
Total Energy (kJ)	-0.00	0.00	-2.76	0.006	-0.00	-0.00			
Total Fat (En%)	0.00	0.01	0.36	0.716	-0.02	0.03			
Sample Size (N)	0.03	0.01	2.07	0.038	0.00	0.05			
Male N (%)	-0.00	0.00	-0.28	0.778	-0.01	0.01			
4-hour model 3									
Intercept	-47.19	45.51	-1.04	0.300	-136.39	42.00	88	89.63	0.360
Age (years)	-0.01	0.01	-0.80	0.424	-0.04	0.02			
BMI (kg/m^2)	0.04	0.06	0.63	0.531	-0.08	0.15			
Fasting FMD%	-0.27	0.07	-4.19	0.000	-0.40	-0.15			
Total Energy (kJ)	-0.00	0.00	-2.06	0.039	-0.00	-0.00			
Total Fat (En%)	0.07	0.01	0.60	0.550	-0.02	0.03			
Sample Size (N)	0.02	0.01	1.72	0.085	-0.00	0.05			
Year	0.02	0.02	1.04	0.297	-0.02	0.07			
4-hour model 3									
Intercept	-61.69	47.46	-1.30	0.194	-154.72	31.33	85	90.01	0.328
Age (years)	-0.01	0.01	-0.54	0.590	-0.04	0.02			
BMI (kg/m^2)	0.05	0.06	0.84	0.399	-0.07	0.17			
Fasting FMD%	-0.28	0.07	-4.16	0.000	-0.41	-0.15			
Total Energy (kJ)	-0.00	0.00	-1.46	0.145	-0.00	0.00			
Total Fat (En%)	0.00	0.01	0.26	0.796	-0.02	0.03			
Male N (%)	-0.00	0.00	-0.35	0.727	-0.01	0.01			
Year	0.03	0.02	1.30	0.193	-0.02	0.08			

Model 1 for each timepoint can be found in the main manuscript. Random-effects meta-regression was conducted by restricted maximum likelihood. BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular disease; En%, percentage of total meal energy; FMD, flow-mediated dilation; FMD%, flow-mediated dilation percent change; kJ, kilojoule; N, sample size; Obs, observations.

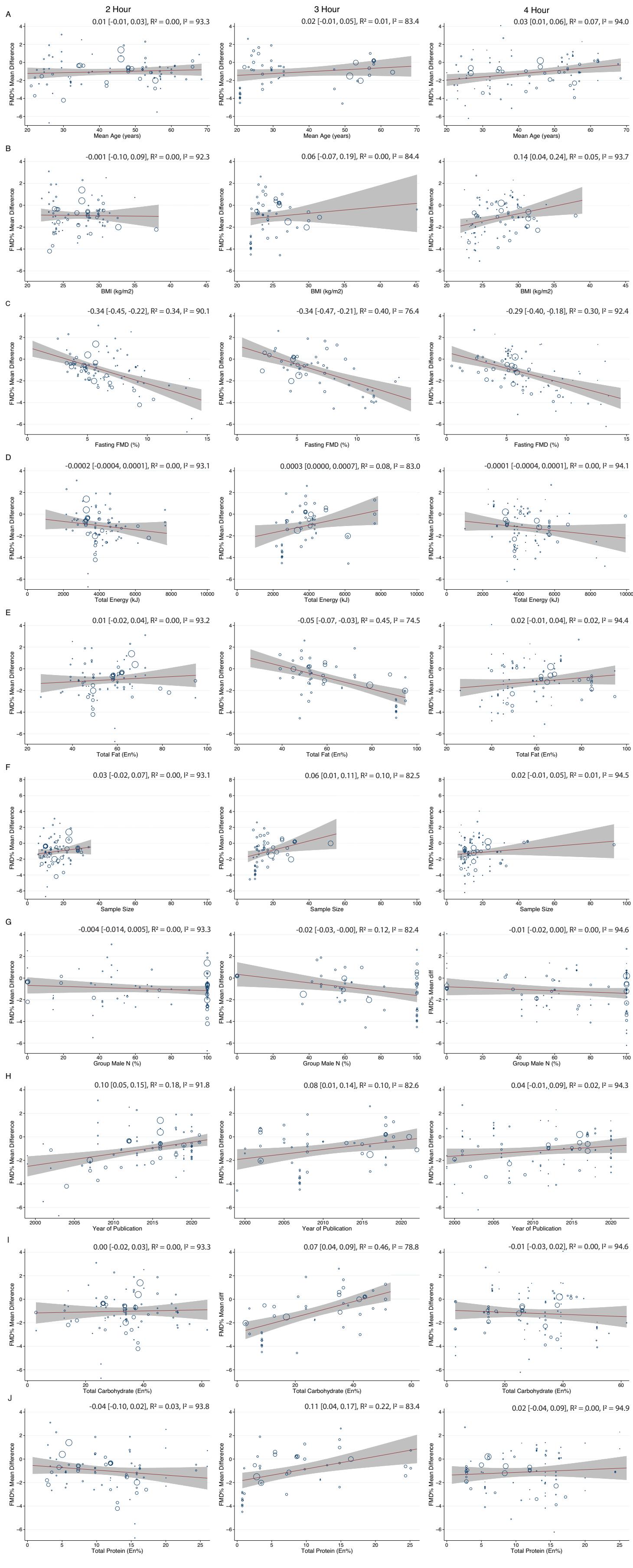


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Supplementary Figure 1. Forest plot of the mean fasting FMD%. Mean FMD% effect size and 95% CIs are indicated by white dots and black horizontal lines. The size of the boxes is proportionally scaled to the effect size for each group in the restricted maximum likelihood model. The red diamond represents the average effect size for all groups. FMD is measured as the relative percent change in peak reactive hyperemia diameter from baseline diameter (FMD%). The heterogeneity analysis is also presented. * Refers to groups with the same participants consuming different meals. # Refers to groups with the same participants consuming the same meal before and after different diet interventions. Abbreviations: CI, confidence interval; En%, percentage of total meal energy; FMD%, flow-mediated dilation percent change.



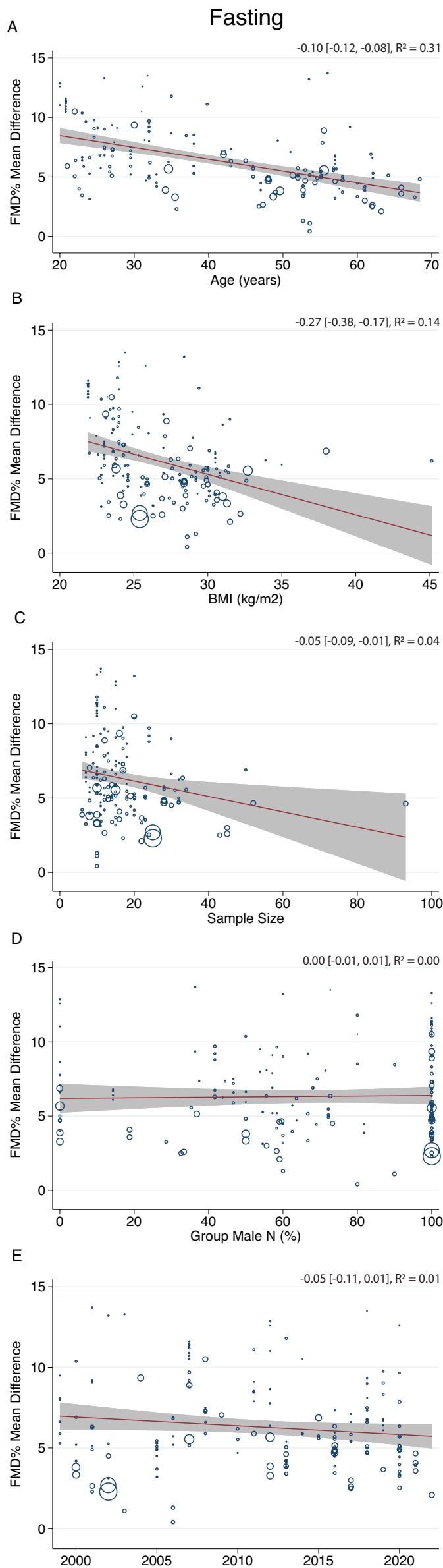
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Supplementary Figure 2. Unadjusted linear regression analysis to evaluate the association of potential modifiers A) age, B) BMI, C) fasting FMD%, D) total meal energy, E) meal fat percentage, F) sample size, G) percentage of male participants, H) year of publication, I) meal carbohydrate percentage, and J) meal protein percentage on the effect of a single high-fat meal on endothelial function. Bubble plot with linear trend line (red line) and 95% CI (grey area). FMD is measured as the relative percent change in peak reactive hyperemia diameter from baseline diameter (FMD%). The mean difference in FMD percentage change was calculated as fasting FMD% subtracted from postprandial FMD%, termed FMD change; the units of which are percentage points (pp). Bubbles are the inverse variance weighted mean difference in FMD% (postprandial-fasting). Coefficient [CI; Lower, Upper], and R² are displayed in the top right-hand corner. Abbreviations: CI, confidence interval; En%, percentage of total meal energy; FMD%, flow-mediated dilation percent change; N, sample size.



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Supplementary Figure 3. Unadjusted linear regression analysis to evaluate the association of potential modifiers A) age, B) BMI, C) sample size, D) percentage of male participants, and E) year of publication on fasting FMD%. Bubble plot with linear trend line (red line) and 95% CI (grey area). FMD is measured as the relative percent change in peak reactive hyperemia diameter from baseline diameter (FMD%). The mean difference in FMD percentage change was calculated as fasting FMD% subtracted from postprandial FMD%, termed FMD change; the units of which are percentage points (pp). Bubbles are the inverse variance weighted mean effect size in fasting FMD%. Coefficient [CI: Lower, Upper], and R² are displayed in the top right-hand corner. Abbreviations: BMI, body mass index; CI, confidence interval; En%, percentage of total meal energy; FMD%, flow-mediated dilation percent change; N, sample size.

A

Study	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Abubakar, 2019 (38)	+	+	+	+	+	+
Alqurashi, 2016 (39)	+	+	+	+	+	+
Anderson, 2006 (42)	-	+	+	+	-	-
Bae, 2003 (46)	-	+	+	+	-	-
Berry, 2008 (49)	-	+	+	+	-	-
Borucki, 2009 (50)	-	+	+	+	X	X
Burton-Freeman, 2012 (52)	-	+	+	+	-	-
Cerriello, 2002 (53)	-	+	+	+	-	-
Cho, 2020 (55)	-	+	+	+	-	-
Cortes, 2006 (56)	-	+	+	+	-	-
Curtis, 2022 (57)	+	+	+	+	-	-
Das, 2018 (58)	-	+	-	+	-	-
deRoos, 2002 (59)	-	+	+	X	X	X
Deveaux, 2016 (60)	+	+	+	+	X	X
do Rosario, 2021 (62)	+	+	+	+	-	-
Esser, 2013 (63)	-	+	+	+	+	-
Evans, 2000 (64)	-	+	+	+	-	-
Fahs, 2010 (66)	-	+	+	+	-	-
Gokce, 2001 (70)	-	+	+	X	-	X
Grassi, 2016 (71)	+	+	+	+	-	-
Hilpert, 2007 (73)	-	+	+	+	-	-
Hodgson, 2005 (74)	-	+	+	+	-	-
Joris, 2013 (77)	-	+	+	+	+	-
Joris, 2020a (78)	-	+	+	+	+	-
Joris, 2020b (79)	-	+	+	+	+	-
Karatazi, 2008 (80)	-	+	+	+	-	-
Katz, 2001 (82)	+	+	+	+	-	-
Krüger, 2016 (84)	-	+	+	+	-	-
Lacroix, 2016 (86)	-	+	+	X	X	X
Lane-Cordova, 2016 (87)	-	+	+	+	-	-
Leary, 2018 (88)	-	+	+	+	-	-
Lin, 2008 (89)	-	+	+	+	-	-
Liu, 2017 (91)	-	+	+	+	+	-
Markey, 2021 (98)	+	+	+	+	-	-
Miyoshi, 2014 (100)	-	+	+	+	-	-
Muggeridge, 2019 (101)	+	+	+	+	+	+
Nagashima, 2011 (103)	+	+	+	+	-	-
Nichols, 2006 (104)	-	+	+	+	-	-
Nijke, 2021 (106)	+	+	+	X	-	X
Noda, 2013 (107)	-	+	+	+	-	-
Ochiai, 2015 (109)	+	+	+	X	-	X
Ohno, 2014 (110)	-	+	+	+	-	-
Papadakis, 2020 (112)	-	+	+	+	-	-
Patlik, 2018 (113)	-	+	+	+	-	-
Petersen, 2020 (114)	+	+	+	+	-	-
Plotnick, 1997 (115)	-	+	+	X	-	X
Plotnick, 2003 (116)	-	+	+	X	-	X
Ramirez-Velez, 2018 (120)	+	+	+	+	+	+
Rathnayake, 2018 (121)	+	X	X	+	+	X
Rendeiro, 2016 (122)	+	X	+	+	-	X
Rouyer, 2019 (123)	-	+	+	+	X	X
Rudolph, 2007 (124)	-	+	+	+	-	-
Rueda-Clausen, 2007 (125)	+	+	+	+	-	-
Salden, 2016 (126)	+	+	+	+	X	X
Sejda, 2002 (128)	-	+	+	+	-	-
Shah, 2017 (129)	-	+	+	+	-	-
Silvestre, 2008 (132)	-	+	+	+	-	-
Smeets, 2020 (134)	+	+	+	+	-	-
Smeets, 2021 (135)	-	+	+	+	-	-
Smolders, 2019 (136)	-	+	+	X	-	X
Stibran, 2010 (137)	+	+	+	+	-	-
Stonehouse, 2015 (138)	+	+	+	+	+	+
Tucker, 2018 (140)	-	+	+	+	-	-
Tushuizen, 2006 (141)	-	+	+	+	-	-
Tylدum, 2009 (143)	-	+	+	+	-	-
van der Made, 2017a (144)	+	+	+	+	-	-
van der Made, 2017b (145)	-	+	+	+	-	-
van Oostrom, 2003 (146)	-	X	X	+	-	X
Volek, 2008 (149)	-	+	+	+	-	-
Volek, 2009 (150)	-	+	+	X	-	X
West, 2005 (151)	-	+	+	+	-	-
Westerink, 2013 (152)	-	+	+	+	-	-
Westphal, 2005 (153)	-	+	+	X	-	X
Westphal, 2009 (154)	-	+	+	X	-	X
Westphal, 2011 (155)	+	+	+	X	-	X
Williams, 1999 (157)	-	+	+	+	-	-
Williams, 2001 (158)	-	+	+	+	-	-
Wilmink, 1999 (159)	-	+	+	+	-	-
Wilmink, 2000 (160)	-	+	+	+	-	-
Wilmink, 2001 (161)	-	+	+	+	-	-
Yunoki, 2011 (163)	-	+	+	+	-	-
Zhang, 2012 (164)	-	+	+	X	-	X
Zhao, 2004 (166)	-	+	+	X	-	X

B

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Anderson, 2001 (40)	-	+	+	+	+	+	-	-
Anderson, 2005 (41)	X	+	+	+	+	+	-	X
Ayer, 2010 (43)	-	+	+	+	+	+	-	-
Bae, 2001a (44)	X	+	+	+	+	+	-	X
Bae, 2001b (45)	X	+	+	+	+	+	-	X
Ballard, 2008 (47)	-	+	+	+	+	+	-	-
Benson, 2018 (48)	-	+	+	+	+	+	-	-
Brook, 2001 (51)	X	+	+	+	+	+	-	X
Chaves, 2009 (54)	X	+	+	+	+	+	-	X
Djoussé, 1999 (61)	X	+	+	+	+	+	-	X
Evans, 2003 (65)	-	+	+	+	+	+	-	-
Fard, 2000 (67)	X	+	+	+	+	+	-	X
Fitschen, 2011 (68)	-	+	+	+	-	+	-	-
Gaenzer, 2001 (69)	-	+	+	+	+	+	X	X
Harris, 2012 (72)	X	+	+	+	+	+	-	X
Jahn, 2016 (75)	X	+	+	+	+	+	-	X
Johnson, 2011 (76)	-	+	+	+	+	+	-	-
Karatazi, 2013 (81)	-	+	+	+	+	+	-	-
Koemel, 2020 (83)	-	+	+	+	+	+	X	X
Kumar, 2021 (85)	-	+	+	+	+	+	-	-
Liu, 2002 (90)	-	+	+	+	+	+	-	-
Maggi, 2004 (92)	-	+	+	+	+	+	-	-
Marchesi, 2000 (93)	-	+	+	+	+	+	-	-
Marchesi, 2001 (94)	-	+	+	+	-	+	-	-
Marchesi, 2002 (95)	-	+	+	+	-	+	-	-
Marchesi, 2003 (96)	-	+	+	+	-	+	-	-
Marinos, 2015 (97)	-	+	+	+	-	+	-	-
McGowan, 2016 (99)	X	+	+	+	+	+	-	X
Muniyappa, 2012 (102)	X	+	+	+	+	+	-	X
Nierman, 2005 (105)	-	+	+	+	+	+	-	-
Norata, 2007 (108)	-	+	+	+	+	+	-	-
Padilla, 2006 (111)	X	+	+	+	+	+	-	X
Poitras, 2014 (117)	-	+	+	+	-	+	-	-
Raitakari, 2000 (118)	X	+	+	+	X	+	-	X
Ramirez-Velez, 2011 (119)	-	+	+	+	-	+	-	-
Schillaci, 2001 (127)	-	+	+	+	+	+	-	-
Shige, 1999 (130)	X	+	+	+	+	+	-	X
Siepi, 2002 (131)	-	+	+	+	+	+	-	-
Skilton, 2005 (133)	-	+	+	+	+	+	-	-
Swift, 2013 (139)	-	+	+	+	?	+	-	-
Tsai, 2004 (22)	-	+	+	+	+	+	-	-
Tushuizen, 2007 (142)	-	+	+	+	?	+	-	-
Verwer, 2020 (147)	-	+	+	+	+	+	-	-
Vogel, 1997 (24)	X	+	+	+	+	+	-	X
Vogel, 2000 (148)	X	+	+	+	+	+	-	X
Widdowson, 2017 (156)	-	+	+	+	-	+	-	-
Xiang, 2012 (162)	X	+	+	+	+	+	-	X
Zhao, 2001 (165)	X	+	+	+	+	+	-	X

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Online Supplementary Material

Supplementary Figure 4. Risk of bias assessment of included A) RCT and B) Non-RCT articles by Cochrane Risk of Bias 2.0 (ROB2.0) and Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool respectively.

For ROB2.0, D1: Bias arising from the randomization process; D2: Bias due to deviations from intended interventions; D3: Bias due to missing outcome data; D4: Bias in measurement of the outcome; D5: Bias in selection of the reported result.

For ROBINS-I, D1: Bias due to confounding; D2: Bias due to selection of participants; D3: Bias in classification of interventions; D4: Bias due to deviations from intended interventions; D5 Bias due to missing data; D6 Bias in measurement of outcomes; D7: Bias in the selection of the reported result.

Green plus symbol denotes low risk of bias, yellow minus symbol denotes moderate risk of bias, red cross symbol denotes high risk of bias, and blue question mark symbol denotes no information.

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McGuinness, LA, Higgins, JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1- 7.

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